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Carvedilol Hydrobromide

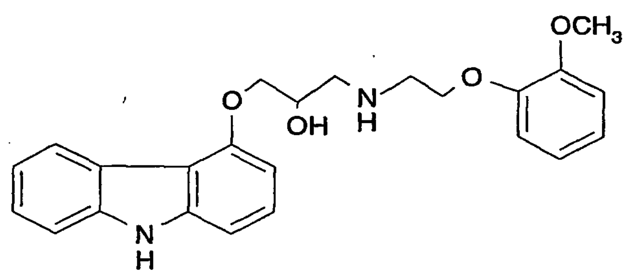
Field of the Invention

The present invention relates to a salt of carvedilol, corresponding compositions containing such a carvedilol salt or corresponding solvates thereof, and/or methods of using the aforementioned compound(s) in the treatment of certain disease states in mammals, in particular man.

The present invention further relates to a novel crystalline form of carvedilol hydrobromide, which is the hydrobromide salt of 1-(carbazol-4-yloxy-3-[[2-(o-methoxyphenoxy)ethyl]amino]-2-propanol, and/or other carvedilol hydrobromide solvates thereof, compositions containing such salts and/or solvates of carvedilol hydrobromide, and methods of using the aforementioned salt(s) and/or solvate(s) to treat hypertension, congestive heart failure, and angina, etc.

Background of the Invention

The compound, 1-(carbazol-4-yloxy-3-[[2-(o-methoxyphenoxy) ethyl]-amino]-2-propanol is known as Carvedilol. Carvedilol is depicted by the following chemical structure:



Carvedilol is disclosed in U.S. Patent No. 4,503,067 to Wiedemann et al. (i.e., assigned to Boehringer Mannheim, GmbH, Mannheim-Waldhof, Fed. Rep. of Germany), which was issued on March 5, 1985.

Currently, Carvedilol is synthesized as free base for incorporation in medication that is available commercially. The aforementioned free base form of Carvedilol is a racemic mixture of R(+) and S(-) enantiomers, where

nonselective β-adrenoreceptor blocking activity is exhibited by the S(-) enantiomer and α-adrenergic blocking activity is exhibited by both R(+) and S(-) enantiomers. Those unique features or characteristics associated with such a racemic Carvedilol mixture contributes to two complementary pharmacologic actions: i.e., mixed venous and arterial vasodilation and non-cardioselective, beta-adrenergic blockade.

Carvedilol is used for treatment of hypertension, congestive heart failure and angina. The currently commercially available carvedilol product is a conventional, tablet prescribed as a twice-a-day medication in the United States.

Carvedilol contains an α-hydroxyl secondary amine functional group, which has a pKa of 7.8. Carvedilol exhibits predictable solubility behaviour in neutral or alkaline media, i.e. above a pH of 9.0, the solubility of carvedilol is relatively low (< 1 μg/mL). The solubility of carvedilol increases with decreasing pH and reaches a plateau near pH = 5, i.e. where saturation solubility is about 23 μg/mL at pH 7 and about 100 μg/mL at pH = 5 at room temperature. At lower pH values (i.e., at a pH of 1 to 4 in various buffer systems), solubility of carvedilol is limited by the solubility of its protonated form or its corresponding salt formed *in-situ*. The hydrochloride salt of carvedilol generated *in-situ* in an acidic medium, such as in a simulated gastric fluid, is less soluble in such medium than the protonated form of carvedilol.

In light of the foregoing, a salt, and/or novel crystalline form of carvedilol (i.e., such as carvedilol hydrobromide monohydrate, carvedilol hydrobromide anhydrate, and/or other solvates thereof) with greater aqueous solubility, chemical stability, etc. would offer many potential benefits for provision of medicinal products containing the drug carvedilol. Such benefits would include products with the ability to achieve desired or prolonged drug levels in a systemic system by sustaining absorption along the gastro-intestinal tract of mammals (i.e., such as humans), particularly in regions of neutral pH, where a drug, such as carvedilol, has minimal solubility.

Surprisingly, it has now been shown that a novel crystalline form of

carvedilol hydrobromide salt, can be isolated as a pure, crystalline solid, which exhibits much higher aqueous solubility than the corresponding free base or other prepared crystalline salts of carvedilol, such as the hydrochloride salt. This novel crystalline form also has potential to improve the stability of carvedilol in formulations due to the fact that the secondary amine functional group attached to the carvedilol core structure, a moiety pivotal to degradation processes, is protonated as a salt.

In light of the above, a need exists to develop different carvedilol forms and/or different compositions respectively, which have greater aqueous solubility, chemical stability, sustained or prolonged drug or absorption levels (i.e., such as in neutral gastrointestinal tract pH regions, etc.).

There also exists a need to develop methods of treatment for hypertension, congestive heart failure or angina, etc. which comprises administration of the aforementioned compounds and/or compositions.

The present invention is directed to overcoming these and other problems encountered in the art.

Summary of the Invention

In general, the present invention relates to a salt of carvedilol, corresponding compositions containing such a carvedilol salt or corresponding solvates thereof, and/or methods of using the aforementioned compound(s) in the treatment of certain disease states in mammals, in particular man.

More specifically, the present invention provides a salt, and/or novel crystalline form of carvedilol hydrobromide (i.e., such as carvedilol hydrobromide monohydrate, carvedilol hydrobromide anhydrate), and/or other solvates thereof.

The present invention further relates to pharmaceutical compositions, which contain the aforementioned salt and/or novel crystalline forms and/or solvates of carvedilol hydrobromide.

The present invention relates to a method of treating hypertension, congestive heart failure or angina, which comprises administering to a subject in need thereof an effective amount of a salt and/or novel crystalline form of carvedilol (i.e., as defined by the aforementioned salts and/or solvates) or a corresponding pharmaceutical composition, which contains such aforementioned salt, and/or novel crystalline forms of carvedilol., etc.

Brief Description of the Figures

Figure 1 is an x-ray powder diffractogram for carvedilol hydrobromide monohydrate.

Figure 2 is a differential scanning calorimetry thermogram for carvedilol hydrobromide monohydrate.

Figure 3 is an FT-Raman spectrum for carvedilol hydrobromide monohydrate.

Figure 4 is an FT-Raman spectrum for carvedilol hydrobromide monohydrate in the 4000-2000 cm^{-1} region of the spectrum.

Figure 5 is an FT-Raman spectrum for carvedilol hydrobromide monohydrate in the 2000-400 cm^{-1} region of the spectrum.

Figure 6 is an FT-IR spectrum for carvedilol hydrobromide monohydrate.

Figure 7 is an FT-IR spectrum for carvedilol hydrobromide monohydrate in the 4000-2000 cm^{-1} region of the spectrum.

Figure 8 is an FT-IR spectrum for carvedilol hydrobromide monohydrate in the 2000-500 cm^{-1} region of the spectrum.

Figure 9 is a view of a single molecule of carvedilol hydrobromide monohydrate. The hydroxyl group and the water molecule are disordered.

Figure 10 are views of molecules of carvedilol hydrobromide monohydrate showing the N-H···Br···H-N interactions. The top view focuses on Br1 and the bottom view focuses on Br2. The interaction between the carvedilol cation and the bromine anion is unusual. Each carvedilol molecule makes two chemically different contacts to the bromine anions. Each bromine anion sits on a crystallographic special position (that is, on a crystallographic two-fold axis) which means that there are two half bromine anions interacting

with each carvedilol cation.

Figure 11 is a differential scanning calorimetry thermogram for carvedilol hydrobromide dioxane solvate.

Figure 12 is an FT-Raman spectrum for carvedilol hydrobromide dioxane solvate.

Figure 13 is an FT-Raman spectrum for carvedilol hydrobromide dioxane solvate in the 4000-2000 cm^{-1} region of the spectrum.

Figure 14 is an FT-Raman spectrum for carvedilol hydrobromide dioxane solvate in the 2000-400 cm^{-1} region of the spectrum.

Figure 15 is an FT-IR spectrum for carvedilol hydrobromide dioxane solvate.

Figure 16 is an FT-IR spectrum for carvedilol hydrobromide dioxane solvate in the 4000-2000 cm^{-1} region of the spectrum.

Figure 17 is an FT-IR spectrum for carvedilol hydrobromide dioxane solvate in the 2000-500 cm^{-1} region of the spectrum.

Figure 18 is a differential scanning calorimetry thermogram for carvedilol hydrobromide 1-pentanol solvate.

Figure 19 is an FT-Raman spectrum for carvedilol hydrobromide 1-pentanol solvate.

Figure 20 is an FT-Raman spectrum for carvedilol hydrobromide 1-pentanol solvate in the 4000-2000 cm^{-1} region of the spectrum.

Figure 21 is an FT-Raman spectrum for carvedilol hydrobromide 1-pentanol solvate in the 2000-400 cm^{-1} region of the spectrum.

Figure 22 is an FT-IR spectrum for carvedilol hydrobromide 1-pentanol solvate.

Figure 23 is an FT-IR spectrum for carvedilol hydrobromide 1-pentanol solvate in the 4000-2000 cm^{-1} region of the spectrum.

Figure 24 is an FT-IR spectrum for carvedilol hydrobromide 1-pentanol solvate in the 2000-500 cm^{-1} region of the spectrum.

Figure 25 is a differential scanning calorimetry thermogram for carvedilol hydrobromide 2-methyl-1-propanol solvate.

Figure 26 is an FT-Raman spectrum for carvedilol hydrobromide 2-methyl-1-propanol solvate.

Figure 27 is an FT-Raman spectrum for carvedilol hydrobromide 2-methyl-1-propanol solvate in the 4000-2000 cm^{-1} region of the spectrum.

Figure 28 is an FT-Raman spectrum for carvedilol hydrobromide 2-methyl-1-propanol solvate in the 2000-400 cm^{-1} region of the spectrum.

Figure 29 is an FT-IR spectrum for carvedilol hydrobromide 2-methyl-1-propanol solvate.

Figure 30 is an FT-IR spectrum for carvedilol hydrobromide 2-methyl-1-propanol solvate in the 4000-2000 cm^{-1} region of the spectrum.

Figure 31 is an FT-IR spectrum for carvedilol hydrobromide 2-methyl-1-propanol solvate in the 2000-500 cm^{-1} region of the spectrum.

Figure 32 is a differential scanning calorimetry thermogram for carvedilol hydrobromide trifluoroethanol solvate.

Figure 33 is an FT-Raman spectrum for carvedilol hydrobromide trifluoroethanol solvate.

Figure 34 is an FT-Raman spectrum for carvedilol hydrobromide trifluoroethanol solvate in the 4000-2000 cm^{-1} region of the spectrum.

Figure 35 is an FT-Raman spectrum for carvedilol hydrobromide trifluoroethanol solvate in the 2000-400 cm^{-1} region of the spectrum.

Figure 36 is an FT-IR spectrum for carvedilol hydrobromide trifluoroethanol solvate.

Figure 37 is an FT-IR spectrum for carvedilol hydrobromide trifluoroethanol solvate in the 4000-2000 cm^{-1} region of the spectrum.

Figure 38 is an FT-IR spectrum for carvedilol hydrobromide trifluoroethanol solvate in the 2000-500 cm^{-1} region of the spectrum.

Figure 39 is a differential scanning calorimetry thermogram for carvedilol hydrobromide 2-propanol solvate.

Figure 40 is an FT-Raman spectrum for carvedilol hydrobromide 2-propanol solvate.

Figure 41 is an FT-Raman spectrum for carvedilol hydrobromide 2-

propanol solvate in the 4000-2000 cm^{-1} region of the spectrum.

Figure 42 is an FT-Raman spectrum for carvedilol hydrobromide 2-propanol solvate in the 2000-400 cm^{-1} region of the spectrum.

Figure 43 is an FT-IR spectrum for carvedilol hydrobromide 2-propanol solvate.

Figure 44 is an FT-IR spectrum for carvedilol hydrobromide 2-propanol solvate in the 4000-2000 cm^{-1} region of the spectrum.

Figure 45 is an FT-IR spectrum for carvedilol hydrobromide 2-propanol solvate in the 2000-500 cm^{-1} region of the spectrum.

Figure 46 is an x-ray powder diffractogram for carvedilol hydrobromide n-propanol solvate #1.

Figure 47 shows the thermal analysis results for carvedilol hydrobromide n-propanol solvate #1.

Figure 48 is an FT-Raman spectrum for carvedilol hydrobromide n-propanol solvate #1.

Figure 49 is an FT-Raman spectrum for carvedilol hydrobromide n-propanol solvate #1 in the 4000-2000 cm^{-1} region of the spectrum.

Figure 50 is an FT-Raman spectrum for carvedilol hydrobromide n-propanol solvate #1 in the 2000-400 cm^{-1} region of the spectrum.

Figure 51 is an FT-IR spectrum for carvedilol hydrobromide n-propanol solvate #1.

Figure 52 is an FT-IR spectrum for carvedilol hydrobromide n-propanol solvate #1 in the 4000-2000 cm^{-1} region of the spectrum.

Figure 53 is an FT-IR spectrum for carvedilol hydrobromide n-propanol solvate #1 in the 2000-500 cm^{-1} region of the spectrum.

Figure 54 is an x-ray powder diffractogram for carvedilol hydrobromide n-propanol solvate #2.

Figure 55 shows the thermal analysis results for carvedilol hydrobromide n-propanol solvate #2.

Figure 56 is an FT-Raman spectrum for carvedilol hydrobromide n-propanol solvate #2.

Figure 57 is an FT-Raman spectrum for carvedilol hydrobromide n-propanol solvate #2 in the 4000-2000 cm^{-1} region of the spectrum.

Figure 58 is an FT-Raman spectrum for carvedilol hydrobromide n-propanol solvate #2 in the 2000-400 cm^{-1} region of the spectrum.

Figure 59 is an FT-IR spectrum for carvedilol hydrobromide n-propanol solvate #2.

Figure 60 is an FT-IR spectrum for carvedilol hydrobromide n-propanol solvate #2 in the 4000-2000 cm^{-1} region of the spectrum.

Figure 61 is an FT-IR spectrum for carvedilol hydrobromide n-propanol solvate #2 in the 2000-500 cm^{-1} region of the spectrum.

Figure 62 is an x-ray powder diffractogram for carvedilol hydrobromide anhydrous.

Figure 63 shows the thermal analysis results for carvedilol hydrobromide anhydrous.

Figure 64 is an FT-Raman spectrum for carvedilol hydrobromide anhydrous.

Figure 65 is an FT-Raman spectrum for carvedilol hydrobromide anhydrous in the 4000-2000 cm^{-1} region of the spectrum.

Figure 66 is an FT-Raman spectrum for carvedilol hydrobromide anhydrous in the 2000-400 cm^{-1} region of the spectrum.

Figure 67 is an FT-IR spectrum for carvedilol hydrobromide anhydrous.

Figure 68 is an FT-IR spectrum for carvedilol hydrobromide anhydrous in the 4000-2000 cm^{-1} region of the spectrum.

Figure 69 is an FT-IR spectrum for carvedilol hydrobromide anhydrous in the 2000-500 cm^{-1} region of the spectrum.

Figure 70 is an x-ray powder diffractogram for carvedilol hydrobromide ethanol solvate.

Figure 71 shows the thermal analysis results for carvedilol hydrobromide ethanol solvate.

Figure 72 is an FT-Raman spectrum for carvedilol hydrobromide ethanol solvate.

Figure 73 is an FT-Raman spectrum for carvedilol hydrobromide ethanol solvate in the 4000-2000 cm^{-1} region of the spectrum.

Figure 74 is an FT-Raman spectrum for carvedilol hydrobromide ethanol solvate in the 2000-400 cm^{-1} region of the spectrum.

Figure 75 is an FT-IR spectrum for carvedilol hydrobromide ethanol solvate.

Figure 76 is an FT-IR spectrum for carvedilol hydrobromide ethanol solvate in the 4000-2000 cm^{-1} region of the spectrum.

Figure 77 is an FT-IR spectrum for carvedilol hydrobromide ethanol solvate in the 2000-500 cm^{-1} region of the spectrum.

Figure 78 is an x-ray powder diffractogram for carvedilol hydrobromide dioxane solvate.

Figure 79 is an x-ray powder diffractogram for carvedilol hydrobromide 1-pentanol solvate.

Figure 80 is an x-ray powder diffractogram for carvedilol hydrobromide 2-methyl-1-propanol solvate.

Figure 81 is an x-ray powder diffractogram for carvedilol hydrobromide trifluoroethanol solvate.

Figure 82 is an x-ray powder diffractogram for carvedilol hydrobromide 2-propanol solvate.

Detailed Description of the Invention

The present invention provides a salt and/or novel crystalline form of carvedilol, i.e., such as carvedilol hydrobromide monohydrate, carvedilol hydrobromide anhydrate, and/or other solvates thereof.

The present invention relates to a pharmaceutical composition, which comprises the aforementioned salts and/or solvates of carvedilol and a pharmaceutically acceptable carrier.

The present invention relates to a method of treating hypertension, congestive heart failure or angina, which comprises administering to a subject in need thereof an effective amount of a salt and/or novel crystalline form of carvedilol (i.e., as defined by the aforementioned salts and/or solvates) or a

corresponding pharmaceutical composition, which contains such aforementioned salt, and/or novel crystalline forms of carvedilol.

Carvedilol is disclosed and claimed in U.S. Patent No. 4,503,067 to Wiedemann et al. ("U.S. '067 Patent"). Reference should be made to U.S. '067 Patent for its full disclosure, which include methods of preparing and/or using the carvedilol compound, etc. The entire disclosure of the U.S. '067 Patent is incorporated hereby by reference in its entirety.

The present invention relates to a compound, which is a salt of carvedilol hydrobromide (such as crystalline carvedilol hydrobromide monohydrate), and/or a carvedilol solvate thereof.

In accordance with the present invention, it has been found unexpectedly that carvedilol hydrobromide can be isolated readily as a novel crystalline form, which displays much higher solubility when compared to the free base of carvedilol.

In particular, crystalline carvedilol hydrobromide monohydrate of the present invention can be prepared by crystallization from an acetone-water solvent system containing carvedilol and hydrobromic acid.

In accordance with the present invention suitable solvates of the instant invention may be prepared by preparing a slurry of the carvedilol hydrobromide salt in a solvent, such as dioxane, 1-pentanol, 2-methyl-1-propanol, trifluoroethanol, 2-propanol and n-propanol.

Suitable solvates of carvedilol as defined in the present invention, include, but are not limited to carvedilol hydrobromide 1-pentanol solvate, carvedilol hydrobromide 2-methyl-1-pentanol solvate, carvedilol hydrobromide trifluoroethanol solvate, carvedilol hydrobromide 2-propanol solvate, carvedilol hydrobromide n-propanol solvate #1, carvedilol hydrobromide n-propanol solvate #2, carvedilol hydrobromide ethanol solvate, carvedilol hydrobromide anhydrate, etc.

In the present invention, carvedilol hydrobromide anhydrate can be prepared by dissolving carvedilol in a solvent, such as dichloromethane, acetonitrile or isopropyl acetate, followed by the addition of anhydrous HBr

(HBr in acetic acid or gaseous HBr).

It is recognized that the compounds of the present invention may exist in forms as stereoisomers, regioisomers, or diastereiomers, etc. These compounds may contain one or more asymmetric carbon atoms and may exist in racemic and optically active forms. For example, carvedilol may exist as as racemic mixture of R(+) and S(-) enantiomers, or in separate respectively optically forms, i.e., existing separately as either the R(+) enantiomer form or in the S(+) enantiomer form. All of these individual compounds, isomers, and mixtures thereof are included within the scope of the present invention.

According to the instant invention, the various forms of carvedilol hydrobromide and/or corresponding solvates are distinguished from each other using different spectroscopic identification techniques, such as Infrared (IR), Raman, Differential Scanning Calorimetry (DSC) and X-ray powder diffraction, etc.

Specifically, a salt or novel crystalline form of carvedilol, which includes carvedilol hydrobromide monohydrate, anhydrate, and/or other solvates thereof, are characterized by spectroscopic data as described below and depicted in Figures 1-82.

For example, crystalline carvedilol hydrobromide monohydrate (see, Example 1: Form 1) is identified by an x-ray diffraction pattern as shown substantially in Figure 1, which depicts characteristic peaks in degrees two-theta (2θ): i.e., 6.5 ± 0.2 (2θ), 10.3 ± 0.2 (2θ), 15.7 ± 0.2 (2θ), 16.3 ± 0.2 (2θ), 19.8 ± 0.2 (2θ), 20.1 ± 0.2 (2θ), 21.9 ± 0.2 (2θ), 25.2 ± 0.2 (2θ), and 30.6± 0.2 (2θ).

Crystalline carvedilol hydrobromide dioxane solvate (see, Example 2: Form 2) also is identified by an x-ray diffraction pattern as shown substantially in Figure 78, which depicts characteristic peaks in degrees two-theta (2θ): i.e., 7.7 ± 0.2 (2θ), 8.4 ± 0.2 (2θ), 15.6 ± 0.2 (2θ), 17.0 ± 0.2 (2θ), 18.7 ± 0.2 (2θ), 19.5 ± 0.2 (2θ), 21.4 ± 0.2 (2θ), 23.7 ± 0.2 (2θ), and 27.9 ± 0.2 (2θ).

Crystalline carvedilol hydrobromide 1-pentanol solvate (see, Example 3: Form 3) also is identified by an x-ray diffraction pattern as shown substantially

in Figure 79, which depicts characteristic peaks in degrees two-theta (2θ): i.e., 77.5 ± 0.2 (2θ), 7.8 ± 0.2 (2θ), 15.2 ± 0.2 (2θ), 18.9 ± 0.2 (2θ), 22.1 ± 0.2 (2θ), and 31.4 ± 0.2 (2θ).

Crystalline carvedilol hydrobromide 2-methyl-1-propanol solvate (see, Example 4: Form 4) also is identified by an x-ray diffraction pattern as shown substantially in Figure 80, which depicts characteristic peaks in degrees two-theta (2θ): i.e., 7.8 ± 0.2 (2θ), 8.1 ± 0.2 (2θ), 16.3 ± 0.2 (2θ), 18.8 ± 0.2 (2θ), 21.8 ± 0.2 (2θ), and 28.5 ± 0.2 (2θ).

Crystalline carvedilol hydrobromide trifluoroethanol solvate (see, Example 5: Form 5) also is identified by an x-ray diffraction pattern as shown substantially in Figure 81, which depicts characteristic peaks in degrees two-theta (2θ): i.e.,. 7.7 ± 0.2 (2θ), 8.4 ± 0.2 (2θ), 15.6 ± 0.2 (2θ), 16.9 ± 0.2 (2θ), 18.9 ± 0.2 (2θ), 21.8 ± 0.2 (2θ), 23.8 ± 0.2 (2θ), 23.7 ± 0.2 (2θ), and 32.7 ± 0.2 (2θ).

Crystalline carvedilol hydrobromide 2-propanol solvate (see, Example 6: Form 6) also is identified by an x-ray diffraction pattern as shown substantially in Figure 82, which depicts characteristic peaks in degrees two-theta (2θ): i.e.,. 7.9 ± 0.2 (2θ), 8.3 ± 0.2 (2θ), 18.8 ± 0.2 (2θ), 21.7 ± 0.2 (2θ), 23.2 ± 0.2 (2θ), 23.6 ± 0.2 (2θ), and 32.1 ± 0.2 (2θ).

Crystalline carvedilol hydrobromide n-propanol solvate #1 (see, Example 7: Form 7) also is identified by an x-ray diffraction pattern as shown substantially in Figure 46, which depicts characteristic peaks in degrees two-theta (2θ): i.e., 7.9 ± 0.2 (2θ), 8.5 ± 0.2 (2θ), 17.0 ± 0.2 (2θ), 18.8 ± 0.2 (2θ), 21.6 ± 0.2 (2θ), 23.1 ± 0.2 (2θ), 23.6 ± 0.2 (2θ), and 21.2 ± 0.2 (2θ).

Crystalline carvedilol hydrobromide n-propanol solvate #2 (see, Example 8: Form 8) also is identified by an x-ray diffraction pattern as shown substantially in Figure 54, which depicts characteristic peaks in degrees two-theta (2θ): i.e., 8.0 ± 0.2 (2θ), 18.8 ± 0.2 (2θ), 21.6 ± 0.2 (2θ), 23.1 ± 0.2 (2θ), 25.9 ± 0.2 (2θ), 27.2 ± 0.2 (2θ), 30.6 ± 0.2 (2θ), and 32.2 ± 0.2 (2θ).

Crystalline carvedilol hydrobromide anhydrous (see, Example 9: Form 9) also is identified by an x-ray diffraction pattern as shown substantially in Figure

62, which depicts characteristic peaks in degrees two-theta (2θ): i.e.,. 6.6 ± 0.2 (2θ), 16.1 ± 0.2 (2θ), 17.3 ± 0.2 (2θ), 21.2 ± 0.2 (2θ), 22.1 ± 0.2 (2θ), 24.1 ± 0.2 (2θ), and 27.9 ± 0.2 (2θ).

Crystalline carvedilol hydrobromide ethanol solvate (see, Example 10: Form 10) also is identified by an x-ray diffraction pattern as shown substantially in Figure 70, which depicts characteristic peaks in degrees two-theta (2θ): i.e., 8.1 ± 0.2 (2θ), 8.6 ± 0.2 (2θ), 13.2 ± 0.2 (2θ), 17.4 ± 0.2 (2θ), 18.6 ± 0.2 (2θ), 21.8 ± 0.2 (2θ), 23.2 ± 0.2 (2θ), 23.7 ± 0.2 (2θ), and 27.4 ± 0.2 (2θ).

Crystalline carvedilol hydrobromide monohydrate further is identified by an infrared spectrum as shown substantially in Figure 6.

Carvedilol hydrobromide anhydrate also an infrared spectrum which comprises characteristic absorption bands expressed in wave numbers as shown substantially in Figure 67.

Crystalline carvedilol hydrobromide monohydrate is identified also by a Raman spectrum as shown substantially in Figure 3.

Carvedilol hydrobromide anhydrate also a Raman spectrum which comprises characteristic peaks as shown substantially in Figure 64.

Further, the present invention relates to pharmaceutical compositions, which contain the aforementioned salt and/or novel crystalline forms and/or solvates of carvedilol hydrobromide.

Importantly, the chemical and/or physical properties of carvedilol forms described herein, which include salt and/or novel crystalline forms of carvedilol, indicate that those forms may be particularly suitable for inclusion in medicinal agents, pharmaceutical compositions, etc.

For example, solubility of various carvedilol salts, anhydrates, and/or solvates as those described herein may facilitate provision or development of a dosage form from which the drug substance becomes available for bioabsorption throughout the gastrointestinal tract (i.e., in particular the lower small intestine and colon). In light of the foregoing, it may be possible to develop stable controlled release dosage forms containing such carvedilol hydrobromide monohydrate, anhydrates and/or solvates, etc., for once-per-day

dosage, delayed release or pulsatile release to optimize therapy by matching pharmacokinetic performance with pharmacodynamic requirements.

Compounds or compositions within the scope of this invention include all compounds or compositions, wherein the compound of the present invention is contained in an amount effective to achieve its intended purpose. While individual needs vary, determination of optimal ranges of effective amounts of each component is within the skill of the art.

Moreover, the quantity of the compound or composition of the present invention administered will vary depending on the patient and the mode of administration and can be any effective amount.

Treatment regimen for the administration of the compounds and/or compositions of the present invention can also be determined readily by those with ordinary skill in art. The quantity of the compound and/or composition of the present invention administered may vary over a wide range to provide in a unit dosage an effective amount based upon the body weight of the patient per day to achieve the desired effect.

In particular, a composition of the present invention is presented as a unit dose and taken preferably from 1 to 2 times daily, most preferably once daily to achieve the desired effect.

Depending upon the treatment being effected, the compounds, and/or or compositions of the present invention can be administered orally, intravascularly, intraperitoneally, subcutaneously, intramuscularly or topically. Preferably, the composition is adapted for oral administration.

In general, pharmaceutical compositions of the present invention are prepared using conventional materials and techniques, such as mixing, blending and the like.

In accordance with the present invention, compounds and/or pharmaceutical composition can also include, but are not limited to, suitable adjuvants, carriers, excipients, or stabilizers, and can be in solid or liquid form such as, tablets, capsules, powders, solutions, suspensions, or emulsions.

Typically, the composition will contain a compound of the present

invention, such as a salt of carvedilol or active compound(s), together with the adjuvants, carriers and/or excipients. In particular, a pharmaceutical composition of the present invention comprises an effective amount of a salt of carvedilol (i.e., such as carvedilol hydrobromide monohydrate), corresponding solvates (i.e., as identified herein) and/or anhydrates (i.e., carvedilol anhydrate) thereof, with any of the characteristics noted herein, in association with one or more non-toxic pharmaceutically acceptable carriers and/or diluents thereof, and if desired, other active ingredients.

In accordance with the present invention, solid unit dosage forms can be conventional types known in the art. The solid form can be a capsule and the like, such as an ordinary gelatin type containing the compounds of the present invention and a carrier, for example, lubricants and inert fillers such as, lactose, sucrose, or cornstarch. In another embodiment, these compounds are tableted with conventional tablet bases such as lactose, sucrose, or cornstarch in combination with binders like acacia, cornstarch, or gelatin, disintegrating agents, such as cornstarch, potato starch, or alginic acid, and a lubricant, like stearic acid or magnesium stearate.

The tablets, capsules, and the like can also contain a binder, such as gum tragacanth, acacia, corn starch, or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, lactose, or saccharin. When the dosage unit form is a capsule, it can contain, in addition to materials of the above type, a liquid carrier such as a fatty oil.

Various other materials may be present as coatings or to modify the physical form of the dosage unit. For instance, tablets can be coated with shellac, sugar, or both. A syrup can contain, in addition to active ingredient, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye, and flavoring such as cherry or orange flavor.

For oral therapeutic administration, these active compounds can be incorporated with excipients and used in the form of tablets, capsules, elixirs,

suspensions, syrups, and the like. The percentage of the compound in compositions can, of course, be varied as the amount of active compound in such therapeutically useful compositions is such that a suitable dosage will be obtained.

Typically in accordance with the present invention, the oral maintenance dose is between about 25 mg and about 50 mg, preferably given once daily. In accordance with the present invention, the preferred unit dosage forms include tablets or capsules.

The active compounds of the present invention may be orally administered, for example, with an inert diluent, or with an assimilable edible carrier, or they can be enclosed in hard or soft shell capsules, or they can be compressed into tablets, or they can be incorporated directly with the food of the diet.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form should be sterile and should be fluid to the extent that easy syringability exists. It should be stable under the conditions of manufacture and storage and should be preserved against the contaminating action of microorganisms, such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol, and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils.

The compounds or pharmaceutical compositions of the present invention may also be administered in injectable dosages by solution or suspension of these materials in a physiologically acceptable diluent with a pharmaceutical adjuvant, carrier or excipients. Such adjuvants, carriers and/or excipients, include, but are not limited to sterile liquids, such as water and oils, with or without the addition of a surfactant and other pharmaceutically and physiologically acceptable carrier, including adjuvants, excipients or stabilizers. Illustrative oils are those of petroleum, animal, vegetable, or synthetic origin, for example, peanut oil, soybean oil, or mineral oil. In general, water, saline,

aqueous dextrose and related sugar solution, and glycols, such as propylene glycol or polyethylene glycol, are preferred liquid carriers, particularly for injectable solutions.

These active compounds may also be administered parenterally. Solutions or suspensions of these active compounds can be prepared in water suitably mixed with a surfactant such as hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof in oils. Illustrative oils are those of petroleum, animal, vegetable, or synthetic origin, for example, peanut oil, soybean oil, or mineral oil. In general, water, saline, aqueous dextrose and related sugar solution, and glycols such as, propylene glycol or polyethylene glycol, are preferred liquid carriers, particularly for injectable solutions. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The compounds and/or compositions prepared according to the present invention can be used to treat warm blooded animals, such as mammals, which include humans.

Conventional administration methods may be suitable for use in the present invention.

The present invention relates to a method for treatment of hypertension, congestive heart failure and angina in a mammal in need thereof, which method comprises administering to said mammal an effective amount of carvedilol hydrobromide monohydrate, or solvates thereof, with any of the characteristics noted herein.

The Examples set forth below are illustrative of the present invention and are not intended to limit, in any way, the scope of the present invention.

Examples

Example 1

Form 1. Carvedilol HBr Monohydrate.

A suitable reactor is charged with acetone. The acetone solution is sequentially charged with carvedilol, water and 48% aqueous HBr. On addition of the water, the acetone slurry becomes a solution. The reaction mixture is stirred at room temperature. A solid precipitates during the course of the stir. The precipitate is filtered and the collected cake is washed with acetone. The cake is dried under vacuum to a constant weight. The cake is weighed and stored in a polyethylene container.

The single crystal x-ray data for carvedilol hydrobromide monohydrate is provided below.

Table 1. Sample and Crystal Data for Carvedilol Hydrobromide Monohydrate.

Crystallization solvents	Acetone, water	
Crystallization method	Slow cooling	
Empirical formula	$C_{24}H_{29}BrN_2O_5$	
Formula weight	505.40	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal size	0.18 x 0.14 x 0.08 mm	
Crystal habit	Clear colorless prism	
Crystal system	Monoclinic	
Space group	C2/c	
Unit cell dimensions	a = 18.0356(3) Å	α= 90°
	b = 20.8385(5) Å	β= 103.5680(10)°
	c = 12.9342(3) Å	γ = 90°
Volume	4725.46(18) $Å^3$	
Z	8	
Density (calculated)	1.421 Mg/m^3	
Absorption coefficient	1.777 mm^{-1}	
F(000)	2096	

Table 2. Data collection and structure refinement for Carvedilol Hydrobromide Monohydrate.

Diffractometer	KappaCCD
Radiation source	Fine-focus sealed tube, MoK_{α}
Data collection method	CCD; rotation images; thick slices
Theta range for data collection	3.42 to 23.27°
Index ranges	$0 \leq h \leq 20$, $0 \leq k \leq 23$, $-14 \leq l \leq 13$
Reflections collected	30823
Independent reflections	3404 [R(int) = 0.042]
Coverage of independent reflections	99.7 %
Variation in check reflections	N/A
Absorption correction	Symmetry-related measurements
Max. and min. transmission	0.8709 and 0.7404
Structure solution technique	Direct methods
Structure solution program	SHELXTL V5.10 UNIX (Bruker, 1997)
Refinement technique	Full-matrix least-squares on F^2
Refinement program	SHELXTL V5.10 UNIX (Bruker, 1997)
Function minimized	$\Sigma w(F_o^2 - F_c^2)^2$
Data / restraints / parameters	3404 / 11 / 336
Goodness-of-fit on F^2	1.020
Δ/σ_{max}	0.000
Final R indices	
3071 data; $I > 2\sigma(I)$	R1 = 0.0353, wR2 = 0.0797
all data	R1 = 0.0405, wR2 = 0.0829
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + [(0.0304P)^2 + 14.1564P]$ where $P = [MAX(F_o^2, 0) + 2F_c^2]/3$
Largest diff. peak and hole	0.786 and -0.914 e.Å^{-3}
Refinement summary:	
Ordered Non-H atoms, XYZ	Freely refined
Ordered Non-H atoms, U	Anisotropic
H atoms (on carbon), XYZ	Idealized positions riding on attached atom
H atoms (on carbon), U	Appropriate constant times Ueq of attached atom
H atoms (on heteroatoms), XYZ	Freely refined
H atoms (on heteroatoms), U	Refined Isotropically
Disordered atoms, OCC	See Table 10
Disordered atoms, XYZ	Refined with distance restaints
Disordered atoms, U	Anisotropic

Table 3. Atomic Coordinates and Equivalent Isotropic Atomic Displacement Parameters (Å^2) for Carvedilol Hydrobromide Monohydrate.

U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x/a	y/b	z/c	U(eq)
Br1	0.5000	0.22079(2)	-0.2500	0.04329(15)
Br2	0.0000	0.40821(2)	-0.2500	0.04510(16)
O1	0.19543(10)	0.37037(10)	-0.00168(15)	0.0328(5)
O2	0.08660(19)	0.48508(15)	0.1085(2)	0.0312(7)
O2'	0.0825(3)	0.4816(3)	-0.0328(4)	0.0311(13)
O3	-0.19428(10)	0.39492(10)	-0.01310(15)	0.0347(5)
O4	-0.24723(12)	0.46974(11)	0.11008(16)	0.0404(5)
O99A	-0.0880(5)	0.4236(3)	0.1967(7)	0.0430(19)
O99B	-0.0833(5)	0.4514(4)	0.1784(7)	0.0431(19)
N1	0.34092(16)	0.25072(13)	-0.1793(2)	0.0390(7)
N2	-0.03151(14)	0.39706(13)	-0.0026(2)	0.0314(6)
C1	0.26859(15)	0.35551(14)	-0.0070(2)	0.0301(7)
C2	0.33380(16)	0.38188(15)	0.0568(2)	0.0339(7)
C3	0.40553(17)	0.36537(16)	0.0409(3)	0.0402(8)
C4	0.41433(17)	0.32249(16)	-0.0364(3)	0.0401(8)
C5	0.34850(16)	0.29538(15)	-0.0986(2)	0.0343(7)
C6	0.26499(17)	0.23737(14)	-0.2202(2)	0.0343(7)
C7	0.23145(19)	0.19604(15)	-0.3022(2)	0.0401(8)
C8	0.15313(19)	0.19096(15)	-0.3275(2)	0.0412(8)
C9	0.10866(18)	0.22594(14)	-0.2721(2)	0.0364(7)
C10	0.14185(17)	0.26731(14)	-0.1910(2)	0.0323(7)
C11	0.22085(16)	0.27356(13)	-0.1639(2)	0.0300(7)
C12	0.27490(16)	0.31103(13)	-0.0855(2)	0.0294(6)
C13	0.18523(16)	0.41746(14)	0.0740(2)	0.0301(7)
C14	0.10181(16)	0.43671(13)	0.0452(2)	0.0305(7)
C15	0.05016(15)	0.37919(14)	0.0363(2)	0.0289(6)
C16	-0.08143(16)	0.33991(14)	-0.0272(2)	0.0361(7)
C17	-0.16200(16)	0.35626(16)	-0.0833(2)	0.0380(7)
C18	-0.27156(15)	0.40680(14)	-0.0445(2)	0.0300(6)
C19	-0.30049(16)	0.44705(14)	0.0236(2)	0.0316(7)
C20	-0.37754(18)	0.46060(16)	0.0007(3)	0.0409(8)
C21	-0.42545(18)	0.43467(17)	-0.0895(3)	0.0499(9)
C22	-0.39733(18)	0.39593(17)	-0.1567(3)	0.0504(9)
C23	-0.31949(17)	0.38199(15)	-0.1342(3)	0.0388(7)
C24	-0.2743(2)	0.50999(17)	0.1833(3)	0.0482(9)

Table 4. Selected Bond Lengths (Å) for Carvedilol Hydrobromide Monohydrate.

O1-C1	1.373(3)	O1-C13	1.428(3)
O2-C14	1.366(4)	O2'-C14	1.360(6)
O3-C18	1.380(3)	O3-C17	1.435(3)
O4-C19	1.376(4)	O4-C24	1.433(4)
N1-C6	1.376(4)	N1-C5	1.381(4)
N2-C16	1.482(4)	N2-C15	1.488(4)
C1-C2	1.382(4)	C1-C12	1.399(4)
C2-C3	1.399(4)	C3-C4	1.378(5)
C4-C5	1.388(4)	C5-C12	1.415(4)
C6-C7	1.389(4)	C6-C11	1.416(4)
C7-C8	1.377(5)	C8-C9	1.399(4)
C9-C10	1.381(4)	C10-C11	1.391(4)
C11-C12	1.458(4)	C13-C14	1.517(4)
C14-C15	1.506(4)	C16-C17	1.503(4)
C18-C23	1.374(4)	C18-C19	1.403(4)
C19-C20	1.380(4)	C20-C21	1.388(5)
C21-C22	1.368(5)	C22-C23	1.396(4)

Table 5. Selected bond angles (°) for Carvedilol Hydrobromide Monohydrate.

C1-O1-C13	118.0(2)	C18-O3-C17	116.5(2)
C19-O4-C24	117.2(2)	C6-N1-C5	109.9(3)
C16-N2-C15	112.0(2)	O1-C1-C2	125.0(3)
O1-C1-C12	115.4(2)	C2-C1-C12	119.6(3)
C1-C2-C3	120.1(3)	C4-C3-C2	122.3(3)
C3-C4-C5	117.1(3)	N1-C5-C4	129.2(3)
N1-C5-C12	108.5(3)	C4-C5-C12	122.4(3)
N1-C6-C7	129.4(3)	N1-C6-C11	108.9(3)
C7-C6-C11	121.7(3)	C8-C7-C6	117.9(3)
C7-C8-C9	121.1(3)	C10-C9-C8	121.0(3)
C9-C10-C11	119.1(3)	C10-C11-C6	119.1(3)
C10-C11-C12	134.7(3)	C6-C11-C12	106.2(3)
C1-C12-C5	118.6(3)	C1-C12-C11	134.8(3)
C5-C12-C11	106.6(3)	O1-C13-C14	107.0(2)
O2'-C14-O2	83.4(3)	O2'-C14-C15	116.4(3)
O2-C14-C15	115.2(3)	O2'-C14-C13	115.6(3)
O2-C14-C13	112.0(3)	C15-C14-C13	111.6(2)
N2-C15-C14	111.8(2)	N2-C16-C17	113.0(3)
O3-C17-C16	108.1(2)	C23-C18-O3	125.0(3)
C23-C18-C19	120.1(3)	O3-C18-C19	114.9(2)
O4-C19-C20	125.4(3)	O4-C19-C18	115.1(2)
C20-C19-C18	119.4(3)	C19-C20-C21	119.8(3)
C22-C21-C20	120.9(3)	C21-C22-C23	119.7(3)
C18-C23-C22	120.0(3)		

Table 6. Hydrogen Bonds and Short C-H···X Contacts for Carvedilol Hydrobromide Monohydrate (Å and °).

D-H···A	d(D-H)	d(H···A)	d(D···A)	<(DHA)
N1-H1N···Br1	0.76(3)	2.53(4)	3.269(3)	166(3)
N2-H2NA···O99A	0.83(4)	2.29(4)	3.037(10)	149(3)
N2-H2NA···O99B	0.83(4)	2.13(4)	2.943(10)	165(4)
N2-H2NB···O2#1	0.89(5)	2.17(4)	2.873(4)	135(4)
O2'-H2O'···Br2	0.67(5)	2.65(7)	3.237(6)	149(12)
O99A-H99A···Br1#2	0.94(3)	2.49(4)	3.395(8)	163(6)
O99B-H99B···Br2#1	0.94(3)	2.38(3)	3.320(8)	173(6)
C15-H15A···O1	0.99	2.38	2.783(3)	103.2
C15-H15B···Br1#2	0.99	2.85	3.738(3)	149.3
C16-H16A···Br1#2	0.99	2.88	3.760(3)	148.2

Symmetry transformations used to generate equivalent atoms:
#1 -x,-y+1,-z #2 -x+1/2,-y+1/2,-z

Table 7. Selected torsion angles (°) for Carvedilol Hydrobromide Monohydrate.

C13-O1-C1-C2	1.2(4)	C13-O1-C1-C12	-177.5(2)
O1-C1-C2-C3	-177.0(3)	C12-C1-C2-C3	1.7(4)
C1-C2-C3-C4	-0.8(5)	C2-C3-C4-C5	-0.5(5)
C6-N1-C5-C4	-179.7(3)	C6-N1-C5-C12	0.8(3)
C3-C4-C5-N1	-178.6(3)	C3-C4-C5-C12	0.8(4)
C5-N1-C6-C7	179.4(3)	C5-N1-C6-C11	-0.9(3)
N1-C6-C7-C8	179.5(3)	C11-C6-C7-C8	-0.1(4)
C6-C7-C8-C9	-0.4(5)	C7-C8-C9-C10	0.8(5)
C8-C9-C10-C11	-0.6(4)	C9-C10-C11-C6	0.0(4)
C9-C10-C11-C12	-179.9(3)	N1-C6-C11-C10	-179.4(3)
C7-C6-C11-C10	0.3(4)	N1-C6-C11-C12	0.6(3)
C7-C6-C11-C12	-179.7(3)	O1-C1-C12-C5	177.4(2)
C2-C1-C12-C5	-1.4(4)	O1-C1-C12-C11	-2.4(5)
C2-C1-C12-C11	178.8(3)	N1-C5-C12-C1	179.6(2)
C4-C5-C12-C1	0.1(4)	N1-C5-C12-C11	-0.5(3)
C4-C5-C12-C11	180.0(3)	C10-C11-C12-C1	-0.3(6)
C6-C11-C12-C1	179.8(3)	C10-C11-C12-C5	179.9(3)
C6-C11-C12-C5	-0.1(3)	C1-O1-C13-C14	166.1(2)
O1-C13-C14-O2'	-82.6(4)	O1-C13-C14-O2	-175.8(2)
O1-C13-C14-C15	53.4(3)	C16-N2-C15-C14	171.3(2)
O2'-C14-C15-N2	-38.6(4)	O2-C14-C15-N2	56.6(3)
C13-C14-C15-N2	-174.2(2)	C15-N2-C16-C17	-170.5(2)
C18-O3-C17-C16	-170.7(2)	N2-C16-C17-O3	-63.3(3)
C17-O3-C18-C23	3.3(4)	C17-O3-C18-C19	-177.3(3)
C24-O4-C19-C20	1.0(4)	C24-O4-C19-C18	-178.7(3)
C23-C18-C19-O4	-179.2(3)	O3-C18-C19-O4	1.4(4)
C23-C18-C19-C20	1.0(4)	O3-C18-C19-C20	-178.3(3)
O4-C19-C20-C21	179.9(3)	C18-C19-C20-C21	-0.4(5)
C19-C20-C21-C22	-0.3(5)	C20-C21-C22-C23	0.3(6)
O3-C18-C23-C22	178.2(3)	C19-C18-C23-C22	-1.1(5)
C21-C22-C23-C18	0.4(5)		

Table 8. Anisotropic Atomic Displacement Parameters (Å^2) for Carvedilol Hydrobromide Monohydrate.

The anisotropic atomic displacement factor exponent takes the form: $-2\pi^2 [h^2a^{*2}U_{11} + ... + 2hka^* b^* U_{12}]$

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
Br1	0.0484(3)	0.0447(3)	0.0464(3)	0.000	0.0306(2)	0.000
Br2	0.0707(3)	0.0413(3)	0.0234(2)	0.000	0.0111(2)	0.000
O1	0.0272(11)	0.0408(12)	0.0323(11)	0.0067(9)	0.0108(9)	-0.0009(9)
O2	0.0416(18)	0.0306(18)	0.0215(17)	-0.0006(14)	0.0077(15)	0.0059(14)
O2'	0.038(3)	0.028(3)	0.031(3)	0.001(3)	0.014(3)	0.000(3)
O3	0.0254(11)	0.0473(13)	0.0308(11)	-0.0091(9)	0.0058(9)	-0.0001(9)
O4	0.0400(12)	0.0500(14)	0.0323(11)	-0.0076(10)	0.0108(10)	0.0019(10)
O99A	0.042(3)	0.044(5)	0.040(4)	-0.004(4)	0.004(3)	0.002(4)
O99B	0.033(3)	0.061(6)	0.035(4)	-0.004(4)	0.007(2)	-0.010(4)
N1	0.0384(17)	0.0449(17)	0.0393(16)	0.0053(13)	0.0203(14)	0.0112(13)
N2	0.0270(13)	0.0341(15)	0.0332(15)	0.0015(13)	0.0075(12)	0.0033(11)
C1	0.0283(16)	0.0324(16)	0.0321(16)	0.0078(13)	0.0124(13)	0.0005(12)
C2	0.0321(17)	0.0381(17)	0.0327(16)	0.0056(13)	0.0100(13)	-0.0014(13)
C3	0.0301(17)	0.048(2)	0.0412(18)	0.0104(16)	0.0051(14)	-0.0044(14)
C4	0.0290(17)	0.0471(19)	0.0470(19)	0.0133(16)	0.0148(15)	0.0064(14)
C5	0.0324(17)	0.0390(17)	0.0343(16)	0.0113(14)	0.0132(14)	0.0065(14)
C6	0.0391(18)	0.0334(17)	0.0339(17)	0.0099(14)	0.0161(14)	0.0088(14)
C7	0.056(2)	0.0324(17)	0.0362(18)	0.0011(14)	0.0204(16)	0.0098(15)
C8	0.055(2)	0.0337(18)	0.0357(18)	-0.0020(14)	0.0119(16)	0.0003(15)
C9	0.0411(18)	0.0344(17)	0.0348(17)	0.0030(14)	0.0111(14)	-0.0009(14)
C10	0.0362(17)	0.0321(16)	0.0323(16)	0.0038(13)	0.0155(14)	0.0022(13)
C11	0.0377(17)	0.0275(15)	0.0277(15)	0.0079(12)	0.0136(13)	0.0040(13)
C12	0.0305(16)	0.0309(16)	0.0295(15)	0.0085(13)	0.0122(13)	0.0017(12)
C13	0.0311(16)	0.0331(16)	0.0265(15)	-0.0019(12)	0.0078(12)	-0.0021(12)
C14	0.0325(16)	0.0307(16)	0.0290(16)	0.0010(13)	0.0083(13)	0.0015(13)
C15	0.0263(15)	0.0327(16)	0.0289(15)	0.0031(12)	0.0090(12)	0.0043(12)
C16	0.0322(16)	0.0347(17)	0.0390(18)	-0.0078(14)	0.0036(14)	0.0016(13)
C17	0.0298(16)	0.0477(19)	0.0342(17)	-0.0106(15)	0.0031(13)	0.0023(14)
C18	0.0246(15)	0.0317(16)	0.0337(16)	0.0031(13)	0.0069(13)	-0.0014(12)
C19	0.0299(16)	0.0352(17)	0.0313(16)	0.0063(13)	0.0103(13)	-0.0031(13)
C20	0.0379(18)	0.0382(18)	0.051(2)	0.0048(15)	0.0194(16)	0.0033(15)
C21	0.0245(17)	0.050(2)	0.073(3)	0.0038(19)	0.0059(17)	0.0012(15)
C22	0.0326(18)	0.053(2)	0.057(2)	-0.0075(18)	-0.0052(16)	-0.0012(16)
C23	0.0317(17)	0.0407(18)	0.0407(18)	-0.0045(14)	0.0021(14)	-0.0004(14)
C24	0.065(2)	0.050(2)	0.0325(18)	-0.0027(15)	0.0176(17)	0.0098(17)

Table 9. Hydrogen Atom Coordinates and Isotropic Atomic Displacement Parameters (Å²) for Carvedilol Hydrobromide Monohydrate.

	x/a	y/b	z/c	U
H2O	0.086(3)	0.471(3)	0.155(4)	0.047
H2O'	0.082(6)	0.465(5)	-0.077(6)	0.047
H99A	-0.073(4)	0.3802(19)	0.201(6)	0.064
H99B	-0.060(4)	0.490(2)	0.205(6)	0.065
H99	-0.1344(19)	0.4409(13)	0.157(3)	0.065
H1N	0.373(2)	0.2411(16)	-0.205(3)	0.039(10)
H2NA	-0.043(2)	0.4188(18)	0.045(3)	0.058(12)
H2NB	-0.036(2)	0.422(2)	-0.060(4)	0.077(14)
H2A	0.3299	0.4112	0.1114	0.041
H3A	0.4497	0.3844	0.0850	0.048
H4A	0.4633	0.3119	-0.0468	0.048
H7A	0.2616	0.1720	-0.3395	0.048
H8A	0.1289	0.1632	-0.3836	0.049
H9A	0.0548	0.2212	-0.2906	0.044
H10A	0.1112	0.2912	-0.1543	0.039
H13A	0.2180	0.4552	0.0713	0.036
H13B	0.1990	0.3994	0.1468	0.036
H14	0.0925	0.4552	-0.0281	0.037
H14'	0.0943	0.4596	0.1099	0.037
H15A	0.0642	0.3477	-0.0132	0.035
H15B	0.0576	0.3585	0.1069	0.035
H16A	-0.0819	0.3172	0.0400	0.043
H16B	-0.0599	0.3103	-0.0723	0.043
H17A	-0.1625	0.3802	-0.1496	0.046
H17B	-0.1922	0.3165	-0.1021	0.046
H20A	-0.3977	0.4876	0.0466	0.049
H21A	-0.4785	0.4439	-0.1048	0.060
H22A	-0.4306	0.3786	-0.2183	0.060
H23A	-0.2996	0.3553	-0.1809	0.047
H24A	-0.2310	0.5242	0.2397	0.072
H24B	-0.3101	0.4858	0.2148	0.072
H24C	-0.3002	0.5475	0.1455	0.072

Table 10. Site Occupation Factors that Deviate from Unity for Carvedilol Hydrobromide Monohydrate.

Atom	sof	Atom	sof	Atom	sof
Br1	1	Br2	1	O1	1
O2	0.65	H2O	0.65	O2'	0.35
H2O'	0.35	O99A	0.50	H99A	0.50
O99B	0.50	H99B	0.50	H99	1
H14	0.65	H14'	0.35		

Example 2

Form 2. Carvedilol HBr (dioxane solvate)

Form 1 is slurried in dioxane between 0 and 40°C for 2 days. The product is filtered and mildly dried.

Example 3

Form 3. Carvedilol HBr (1-pentanol solvate)

Form 1 is slurried in 1-pentanol between 0°C and 40°C for 2 days. The product is filtered and mildly dried.

Example 4

Form 4. Carvedilol HBr (2-Methyl-1-Propanol solvate)

Form 1 is slurried in 2-Methyl-1-Propanol between 0°C and 40°C for 2 days. The product is filtered and mildly dried.

Example 5

Form 5. Carvedilol HBr (trifluoroethanol solvate)

Form 1 is slurried in trifluoroethanol between 0°C and 40°C for 2 days. The product is filtered and mildly dried.

Example 6

Form 6. Carvedilol HBr (2-propanol solvate)

Form 1 is slurried in 2-propanol between 0°C and 40°C for 2 days. The product is filtered and mildly dried.

Example 7

Form 7. Carvedilol HBr (n-propanol solvate #1)

Carvedilol free base is dissolved in n-propanol/water (95:5), and stoichiometric hydrobromic acid is added. The solution is cooled, and crystallization ensues. The product is filtered, washed with process solvent, and dried.

Example 8

Form 8. Carvedilol HBr (n-propanol solvate #2)

Carvedilol HBr monohydrate (Form 1) is dissolved in n-propanol at ambient temperature. The n-propanol is slowly evaporated off, giving a white solid.

Example 9

Form 9. Carvedilol HBr (anhydrous and solvent free)

Carvedilol free base is dissolved in a solvent (dichloromethane, isopropyl acetate, and acetonitrile have been used) and anhydrous HBr is added (HBr in acetic acid or gaseous HBr). The solution is cooled, and crystallization ensues. The product is filtered, washed with process solvent, and dried.

Example 10

Form 10. Carvedilol HBr (ethanol solvate)

Carvedilol free base is dissolved in ethanol, and anhydrous HBr is added (HBr in acetic acid). The solution is cooled, and crystallization ensues. The product is filtered, washed with process solvent, and dried.

It is to be understood that the invention is not limited to the embodiments illustrated herein. The right is reserved to the illustrated embodiments and all modifications coming within the scope of the following claims.

The various references to journals, patents, and other publications which are cited herein comprise the state of the art and are incorporated herein by reference as though fully set forth.